EUROPEAN CHEMICALS AGENCY

Helsinki, 20 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449729-32-01/F
Substance name: 12H-phthaloperin-12-one
EC number: 230-049-5
CAS number: 6925-69-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10 May 2013
Registered tonnage band: 10-100 (submission number: [redacted] with tonnage band).

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information generated with a test material representative of the Substance on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471);**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487);**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490); provided that both studies requested under 1. and 2. have negative results;**

You are required to submit the requested information in an updated registration dossier by **27 November 2019**.

You are required to submit the results in a form of a robust study summary[1]. You shall also update the chemical safety report. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.
The scope of this compliance check decision is limited to the standard toxicological information requirements of Annex VIII to the REACH Regulation.

[1] See ECHA Practical guide 3: https://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf/

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Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[2] by Ofelia Bercaru, Head of Unit, Evaluation E3

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for the endpoints addressed in this Decision, adaptation arguments either in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation and/or of predictions generated with the use of QSAR models under Annex XI, Section 1.3 of the REACH Regulation. Furthermore you have indicated that the information provided is adequate for Weight of Evidence.

ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

1. For the use of read-across approach according to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Unambiguous substance identity for both the source substance and tha target substance is therefore a prerequisite for a read-across assessment. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data on reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

   Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[3]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.
   Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

2. For the use of (Q)SAR models, according to Annex XI, Section 1.3, the results obtained from valid (Q)SAR models may be used instead of testing when the following conditions are met[4]:
   - results are derived from a (Q)SAR model whose scientific validity has been established,
   - the substance falls within the applicability domain of the (Q)SAR model,
   - results are adequate for the purpose of classification and labelling and/or risk

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

assessment, and
- adequate and reliable documentation of the applied method is provided.

3. For the use of adaptations using Weight of Evidence (WoE), according to Annex XI, Section 1.2., it is required that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to the specific standard information requirement.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

For your registration an *In vitro* gene mutation study in bacteria is a standard information requirement.

You have indicated "(Q)SAR" in the administrative section of one endpoint study record in the technical dossier for "in vitro gene mutation in bacteria". In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox and it is indicated within this report that it is used to predict gene mutation for the registered substance based on read-across. In addition, you claimed read-across to phthalimide (CAS number: 85-41-6) for this endpont quoting OECD SIDS assessment report as the data source.

ECHA notes that:

1. You have not provided an assessment to address structural similarity/dissimilarity between the registered substance and the proposed analogue(s).
2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the registered substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across, and
4. The endpoint study records fields have not been filled in.

You have further provided within the Endpoint Study Summary for "Genetic Toxicity in vitro" a statement that "From the various data, it is seen that the target chemical as well as the read-across chemical are unlikely to exhibit genetic toxicity effects.".

ECHA notes that, for the reasons explained above, the information provided as explained in Sections 1, 2 and 3 of this Appendix, do not constitute relevant and reliable information in the context of a weight of evidence approach.

ECHA therefore concludes that:

- The proposed adaptation is not in line neither with the conditions specified in Annex XI, Section 1.5., nor with those specified in Annex XI, Section 1.2. and is therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

In your comments to the draft decision you agreed to perform this test.

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

For your registration, an *In vitro* cytogenicity study in mammalian cells or in vitro micronucleus study in a standard information requirement.

You have indicated "(Q)SAR" in the administrative section of the endpoint study record in the technical dossier for "in vitro cytogenicity / chromosome aberration study in mammalian cells". In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox and it is indicated within this report that it is used to predict chromosome aberration for the registered substance based on read-across.

ECHA notes that:

1. You have not provided an assessment to address structural similarity/dissimilarity between the registered substance and the proposed analogue(s).
2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the registered substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across, and
4. The endpoint study records fields have not been filled in.

You have further provided within the Endpoint Study Summary for "Genetic Toxicity in vitro" a statement that "From the various data, it is seen that the target chemical as well as the read-across chemical are unlikely to exhibit genetic toxicity effects.".

ECHA notes that, for the reasons explained above, the information provided as explained in Sections 1, 2 and 3 of this Appendix, do not constitute relevant and reliable information in the context of a weight of evidence approach.

ECHA therefore concludes that:

- The proposed adaptation is not in line neither with the conditions specified in Annex XI, Section 1.5., nor with those specified in Annex XI, Section 1.2. and is therefore rejected.

- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

In your comments to the draft decision you agreed to perform this test.

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

For your registration an *In vitro* gene mutation study in mammalian cells is a standard information requirement if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained. Currently your dossier does not have acceptable information on the two endpoints mentioned above. Adequate information on *in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under 1 and 2 have negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision you indicated that this study is not a data requirement for registrations at 10-100 tonnes per year. As explained above, an *in vitro* gene mutation study in mammalian cells is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

Also, you indicate that "*since after above test there will be data available for the substance which may confirms that the substance not genetically toxic substance*". ECHA considers this statement outlines a future intention. No further data available on this endpoint, submitted by you.

Therefore, adequate information for this endpoint needs to be present if the studies requested under 1 and 2 of this draft decision give negative results.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a Sub-chronic toxicity study (90-day) and a Prenatal developmental toxicity study in the first species. Due to the tonnage band change, these two requests have been removed from the present decision. As a consequence, the deadline for providing the information to meet the requests remaining in the draft decision has been set to 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. However, following your comments on the draft decision indicating a tonnage band downgrade, you have updated your dossier on two occasions: First occasion - revised tonnage band in submission number [redacted] submission date 31 May 2018 for 2015 – 2017, only; Second occasion - indicated that you had updated some data in submission number [redacted] submission date 9 July 2018. ECHA observed that all the tonnage volumes were not stated. ECHA considers this accidental and that you will re-instate the tonnage volumes following a future dossier update, however, consequentially, ECHA has taken into account the updated tonnage band, as outlined in submission number, [redacted]. No assessment of the updated registration dossiers has occurred. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band as basis for the draft decision from 100 – 1000 tonnes per year (submission number: [redacted] (submission date 10 May 2013)) to 10 – 100 tonnes per year (submission number: [redacted]).

The compliance check was initiated on 16 January 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and your information about a tonnage band downgrade.

This has resulted in the removal of the following decision requests: Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats, and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.